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Time to revisit the definition and clinical criteria for anaphylaxis?

Paul J. Turner^{a,b,*}, Margitta Worm^c, Ignacio J. Ansotegui^d, Yehia El-Gamal^e,
Montserrat Fernandez Rivas^f, Stanley Fineman^g, Mario Geller^h, Alexei Gonzalez-Estradaⁱ,
Paul A. Greenberger^j, Luciana K. Tanno^{k,l,m}, Mario Sánchez Borgesⁿ, Gianenrico Senna^o,
Aziz Sheikh^p, Bernard Y. Thong^q, Motohiro Ebisawa^r and Victoria Cardona^s, On behalf of the
WAO Anaphylaxis Committee

Anaphylaxis represents the severe end of the spectrum of allergic reactions. A number of different definitions for anaphylaxis are currently found in the literature (Table 1).¹⁻⁶ Many define anaphylaxis as a life-threatening reaction. However, data from large case series and patient registries have demonstrated that despite the fact that the vast majority of anaphylaxis reactions are not treated appropriately with prompt administration of epinephrine/adrenaline, in general this does not result in increased mortality or morbidity (such as hospitalization)⁷⁻⁹; this observation is also consistent with national epidemiological data for food anaphylaxis, which indicate that fatal anaphylaxis is a rare (but unpredictable) event.¹⁰⁻¹² Therefore, the majority of anaphylaxis reactions cannot be described as life-threatening in themselves, although due to our inability to predict severity of reaction,¹² we emphasize that all anaphylaxis must be appropriately treated with intramuscular epinephrine/adrenaline. Both the descriptions used by the Australasian Society of Clinical Immunology and Allergy (ASCI)⁴ and National Institute of Allergy and Infectious Disease (NIAID)⁵ refer to anaphylaxis as a serious

allergic reaction, and acknowledge the spectrum of severity in terms of identifying the potential for anaphylaxis to be life-threatening.

In 2005, the Second NIAID/Food Allergy and Anaphylaxis Network symposium proposed clinical criteria for diagnosing anaphylaxis,⁵ which were subsequently adopted by the World Allergy Organization (Table 2).¹ Of note, these criteria are not a definition, but rather, an aid to diagnosis. At the time, it was acknowledged that the criteria were designed to correctly identify at least 95% of anaphylaxis (i.e. with a sensitivity of >95%); however, the authors identified the “need to establish their utility and determine whether there is need for further refinement in prospective multicenter clinical surveys”.⁵

The passage of time is testament to the utility of these criteria for diagnosis and research, however more recently it has become clear that some refinement to the above definitions and criteria might be helpful (as acknowledged in the original publication). In particular, the concept of equating anaphylaxis with a systemic or multi-organ reaction is potentially problematic. This is because:

- **Anaphylaxis often involves isolated respiratory or cardiovascular symptoms:** in a large prospective cohort of anaphylaxis presenting to an emergency department, 31% and 14% of cases had isolated respiratory or cardiovascular symptoms in isolation, respectively.¹³ Indeed, such a presentation is not uncommon in fatal anaphylaxis, both due to food and other allergens,^{14,15} and is becoming increasingly recognised in the context of oral immunotherapy, yet by the current NIAID/FAAN

^aNational Heart & Lung Institute, Imperial College London, London, UK

*Corresponding author. National Heart & Lung Institute, Imperial College London, Norfolk Place, London W2 1PG, United Kingdom Email: p.turner@imperial.ac.uk

Full list of author information is available at the end of the article

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WAO ¹	EAACI ²	AAAAI/ACAAI ³	ASCI ⁴	NIAID ⁵	WHO ICD-11 ⁶
A serious life-threatening generalized or systemic hypersensitivity reaction. A serious allergic reaction that is rapid in onset and might cause death	A severe life-threatening generalized or systemic hypersensitivity reaction. An acute, potentially fatal, multi-organ system, allergic reaction.	An acute life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden release of mediators from mast cells and basophils.	Anaphylaxis is a serious, rapid-onset, allergic reaction that may cause death. Severe anaphylaxis is characterized by life-threatening upper airway obstruction, bronchospasm and/or hypotension.	Anaphylaxis is a serious allergic reaction that involves more than one organ system (for example, skin, respiratory tract, and/or gastrointestinal tract). It can begin very rapidly, and symptoms may be severe or life-threatening.	Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes.

Table 1. Current definitions of anaphylaxis in the literature

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
 - a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after expo sun; *to a likely allergen for that patient* (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP^a
 - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Table 2. Clinical criteria for the diagnosis of anaphylaxis, proposed at the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) symposium, 2005. PEF, *Peak expiratory flow*; BP, *blood pressure*. a. Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years

criteria, reactions with only respiratory symptoms do not meet the criteria for diagnosing anaphylaxis.

- It is difficult to describe isolated respiratory symptoms as generalized or systemic. If an allergen provokes acute bronchoconstriction that is life-endangering in the absence of

other symptoms, then anaphylaxis must be considered as a diagnosis and, more importantly, the reaction should be managed accordingly.

- Allergic reactions may, for example, involve skin manifestations remote to the site of allergen exposure - and are therefore almost certainly a

systemic manifestation - but in the absence of other symptoms such reactions would not necessarily be classified as anaphylaxis. Furthermore, there is emerging evidence that even mild, non-generalized allergic reactions can involve underlying systemic immune activation. Therefore, not all systemic reactions are currently classified as anaphylaxis.¹⁶

- Some triggers of anaphylaxis cause rapidly progressing symptoms, but are of delayed onset after allergen exposure e.g. alpha-gal, in which reactions can occur up to 10 hours after allergen ingestion.¹⁷

The lack of definition for “persistent” when applied to gastrointestinal symptoms in the current NIAID/FAAN framework (Table 2) is unhelpful: is “persistent” 10, 20, 60 minutes, or even longer? This matters in terms of patient management, clinical audit and research - does an allergic reaction resulting in persistent nausea and skin symptoms constitute anaphylaxis? Should a patient who develops generalized urticaria and vomiting after an insect sting or subcutaneous immunotherapy be treated as anaphylaxis, as according to the current criteria such symptoms would need to become persistent to meet the definition of anaphylaxis.

There has long been a discrepancy between the inclusion of gastrointestinal symptoms as a defining feature of food-induced anaphylaxis in North America, but not in Australia¹⁸ or the United Kingdom,¹⁹ on the basis that with food allergens, gastrointestinal symptoms are the result of local allergen exposure (as opposed to the same symptoms resulting from parenteral exposure, which would be considered to represent

anaphylaxis). Thus, reactions to food allergens involving skin and gastrointestinal symptoms would not be termed anaphylaxis in these regions, and would not usually be treated with epinephrine/adrenaline. This lack of consistency creates significant methodological issues when undertaking research to better understand the response (or lack of) to rescue treatment etc., hampering improvements in anaphylaxis care.

Therefore, the Anaphylaxis Committee of the World Allergy Organization (WAO) propose the following revisions to the definition and criteria relating to anaphylaxis:

A REVISED DEFINITION FOR ANAPHYLAXIS

“Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in breathing and/or the circulation, and may occur without typical skin features or circulatory shock being present.”

Rationale: Anaphylaxis lies along the spectrum of severity in terms of the extent of symptoms (Fig. 1), ranging from mild-moderate respiratory symptoms to circulatory “shock” and/or collapse (“anaphylactic shock”). This description encompasses a more nuanced approach, consistent with the evidence base relating to severe and fatal anaphylaxis, that not every anaphylaxis reaction is life-threatening. However, given our inability to predict severe reactions and evidence that



Mild, localized
symptoms

Generalized allergic
reaction

Anaphylaxis

Severe
anaphylaxis

Fig. 1 Spectrum of symptom severity in hypersensitivity reactions and anaphylaxis. Images courtesy of Pete Smith, MBBS, PhD, Medical Media Kits; informed consent received.

early adrenaline may help reduce risk,¹² all anaphylaxis reactions (irrespective of severity) demand appropriate treatment with intramuscular epinephrine/adrenaline. The description also highlights the possibility of anaphylaxis occurring in the absence of skin involvement or cardiovascular shock.¹⁴

A REFINEMENT OF THE WAO/NIAID/FAAN CLINICAL CRITERIA FOR THE DIAGNOSIS OF ANAPHYLAXIS

The WAO Anaphylaxis Committee propose to amend the current NIAID/FAAN criteria, as shown in Table 3. Our aim is to simplify the existing criteria, by combining the first two NIAID/FAAN criteria and modifying the third to give 2 scenarios:

1. Typical skin symptoms AND significant symptoms from at least 1 other organ system; OR
2. Exposure to a known or probable allergen for that patient, with respiratory and/or cardiovascular compromise.

Rationale: Given the uncertainty over the definition of “persistent” gastrointestinal symptoms discussed above, this wording has been modified to “severe gastrointestinal symptoms (e.g. severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens”. This acknowledges that gastrointestinal symptoms, particularly after exposure to non-food allergens,

are indicative of anaphylaxis, without requiring such symptoms to become persistent in order to be treated appropriately. The choice of “severe” rather than “persistent” is also consistent with the grading system for allergic reactions used within the US-based Consortium of Food Allergy Research (CoFAR).²⁰

The second criterion reflects the reality that the occurrence of objective respiratory signs in isolation following exposure to a known allergen, is indicative of anaphylaxis.

Importantly, these criteria do not preclude the treatment of early, but potentially evolving systemic reactions in the context of allergen immunotherapy (particularly via the sub-cutaneous route) as anaphylaxis.

SUMMARY

The WAO Anaphylaxis Committee present to our global colleagues the above definition and clinical criteria for the diagnosis of anaphylaxis, our aim being to better capture the reality of anaphylaxis presentations, simplify diagnosis and therefore improve the management of anaphylaxis.

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None.

Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING:
 - a. Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
 - c. Severe gastrointestinal symptoms (e.g. severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens
2. Acute onset of hypotension* or bronchospasm or laryngeal involvement^a after exposure to a known or highly probable allergen^b for that patient (minutes to several hours^c), even in the absence of typical skin involvement.

Table 3. Amended criteria for the diagnosis of anaphylaxis, proposed by the WAO Anaphylaxis Committee, 2019. PEF, Peak expiratory flow; BP, blood pressure. *Hypotension defined as a decrease in systolic BP greater than 30% from that person's baseline, OR i. Infants and children under 10 years: systolic BP less than $(70 \text{ mmHg} + [2 \times \text{age in years}])$; ii. Adults: systolic BP less than $<90 \text{ mmHg}$. a. Laryngeal symptoms include: stridor, vocal changes, odynophagia. b. An allergen is a substance (usually a protein) capable of triggering an immune response that can result in an allergic reaction. Most allergens act through an IgE-mediated pathway, but some non-allergen triggers can act independent of IgE (for example, via direct activation of mast cells). c. The majority of allergic reactions occur within 1–2 hours of exposure, and usually much quicker. Reactions may be delayed for some food allergens (e.g. alpha-gal) or in the context of immunotherapy, occurring up to 10 hours after ingestion.”

Conflict of interest

All authors have completed ICMJE declarations regarding conflict of interest. This article is written on behalf of the WAO Anaphylaxis Committee, the authors have no other relevant conflicts of interest.

Consent for publication

All authors provided input into the manuscript, reviewed the final draft and provided consent for publication.

Ethics approval

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Author details

^aNational Heart & Lung Institute, Imperial College London, London, UK. ^bDiscipline of Paediatrics and Child Health, School of Medicine, University of Sydney, Sydney, Australia. ^cDepartment of Dermatology and Allergology, Charité-Universitätsmedizin, Berlin, Germany. ^dDept. Allergy and Immunology, Hospital Quironsalud Bizkaia, Bilbao, Spain. ^ePediatric Allergy and Immunology Unit, Ain Shams University, Cairo, Egypt. ^fServicio de Alergia, Hospital Clínico San Carlos, IdISSC, Madrid, Spain. ^gDepartment of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA. ^hDivision of Medicine, Academy of Medicine of Rio de Janeiro, Rio de Janeiro, Brazil. ⁱDivision of Pulmonary, Allergy and Sleep Medicine, Department of Medicine, Mayo Clinic, Jacksonville, FL, USA. ^jDivision of Allergy-Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. ^kHospital Sírio Libanês, São Paulo, Brazil. ^lUniversity Hospital of Montpellier, Montpellier. ^mSorbonne Universités, Paris, France. ⁿAllergy and Clinical Immunology Department, Centro Médico Docente La Trinidad, Caracas, Venezuela. ^oAsthma Center and Allergy Unit, Verona University and General Hospital, Verona, Italy. ^pAllergy and Respiratory Research Group, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK. ^qDepartment of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore. ^rDepartment of Allergy, Clinical Research Center for Allergy and Rheumatology, Sagami-hara National Hospital, Kanagawa, Japan. ^sAllergy Section, Department of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Spain.

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